## REMARKS

Rejection of Claims 3-4, 7-8 and 11-12 Under 35 U.S.C. 112, first paragraph

Claims 3-4, 7-8 and 11-12 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "[t]he monoclonal antibody cA2 recited in claims 3-4, 7-8 and 11-12 are essential to the claimed invention," and that a deposit is required.

Pursuant to 37 C.F.R. §1.809 (b)(1), Applicant will make an acceptable deposit before or with the payment of the issue fee.

Item 5: Rejections of Claims 1-12 Under 35 U.S.C. § 103

Claims 1-12 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,698,195 (Le '195 patent) in view of Shah *et al.* and Lukacs *et al.* (*J. Immunol.*, 154:5411-5417 (1995)). Applicant respectfully disagrees that Claims 1-12 are obvious in view of the cited references.

*Teachings of the Cited References*

Le '195 Patent

In Paper No. 5, the Le '195 patent had been cited by the Examiner as teaching "a chimeric antibody cA2, which has high affinity, epitope specificity and the ability to neutralize the cytotoxic effects of human TNF-α" (Paper no. 5, at page 5, lines 5-7). In Paper No. 5, the Le '195 patent had also been cited by the Examiner as teaching "the use of a therapeutically effective amount of the cA2 antibody in treating a subject (i.e. an individual) having a pathology associated with abnormal levels of TNF-α, when compared with the levels of TNF-α in a normal healthy subject" (Paper no. 5, at page 5, lines 7-10).

Shah *et al.*

The Shah *et al.* reference is discussed in detail above. In summary, the Shah *et al.* reference is a review article summarizing the scientific rationale in 1995 that supported TNFα as an attractive target for asthma. However, although Shah *et al.* report information from both *in*

*vitro* and *in vivo* human and mouse studies, no data were disclosed showing that blocking TNFα would treat asthma. Thus, while Shah *et al.* express hope that an anti-TNFα antibody would provide a new type of therapeutic intervention in the treatment of asthma, the cited reference does not teach or suggest that clinical benefit would in fact occur.

At best, Shah *et al.* invite one of ordinary skill in the art to explore "the possibility of a new type of therapeutic intervention" in the treatment of asthma. In particular, Shah *et al.* invite one of ordinary skill in the art to explore the possibility of an anti-TNFα antibody as a new type of therapeutic intervention in the treatment of asthma.

Lukacs *et al.*

Lukacs *et al.* describe a study designed to examine the role of TNF in the initiation and maintenance of leukocyte recruitment in airway inflammation induced by intratracheal challenge with soluble parasite (*Schistosoma mansoni*) egg Ag (SEA). The SEA-induced airway inflammation model used by Lukacs *et al.* is a model of Th2 cell-induced eosinophilic airway inflammation that allows for the study of the recruitment of various leukocyte subsets to lungs and airways (Lukacs *et al.*, page 5412, column 1, lines 12-16). This model of airway inflammation is characterized as having both an early neutrophilic (8-h) and a later (48-h) eosinophilic airway infiltration (Lukacs *et al.*, page 5415, column 2, last paragraph).

Lukacs *et al.* found that TNF mRNA expression and protein production were observed early during SEA-induced airway inflammation, and subsequently decreased to levels observed in vehicle-control-treated animals (Lukacs *et al.*, page 5415, column 2, last paragraph). Lukacs *et al.* also found that intratracheal SEA-challenged mice treated with the TNF receptor sTNFr-:Fc demonstrated significantly decreased recruitment of neutrophils and eosinophils into the lung and airway. The authors concluded that the results indicate that TNF-α mediates the recruitment of neutrophils and eosinophils during SEA-induced airway inflammation.

However, Lukacs *et al.* treated mice with a TNF receptor, not with an anti-TNF antibody. One of ordinary skill in the art would not reasonably have predicted given the results obtained by Lukacs *et al.* using a TNF receptor that an anti-TNF antibody could be used, with a reasonable expectation of success, in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

Recent papers have been published reporting that TNF-α plays a central role in asthma and airway inflammation, while other recent papers have been published reporting that TNF does not have a critical proinflammatory role in asthma or airway inflammation. For example, Rudmann *et al.* (*Am. J. Physiol. Lung Cell Mol. Physiol.*, 279:L1047-L1057 (2000) (see Amendment filed on November 18, 2004 Exhibit 1)) demonstrated that blockade of TNF bioactivity did not abrogate allergic inflammation in mice deficient in TNF receptors and in wildtype mice treated with anti-TNF neutralizing antibody. However, Matheson *et al.* (*Am. J. Respir. Cell Mol. Biol.*, 27:396-405 (2002); see Amendment filed on November 18, 2004 Exhibit 2)) report that the role of TNF-α in toluene diisocynate (TDI)-induced asthma was demonstrated in TNF-α-deficient mice, produced by either administration of neutralizing antibodies or by deletion of the gene controlling TNF receptors, with the abatement of TDI-induced airway hyperresponsiveness and inflammation, but not specific antibody formation. These recent papers provide evidence that one of ordinary skill in the art would not have been able to predict given the teachings of Lukacs *et al.* whether administration of an anti-TNF antibody to a subject would be effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

*Combination of References*

As discussed above, the Le '195 patent teaches the use of a therapeutically effective amount of the cA2 antibody in treating a subject having a pathology associated with abnormal levels of TNF-α, when compared with the levels of TNF-α in a normal healthy subject. Shah *et al.* invite one of ordinary skill in the art to explore the possibility of an anti-TNFα antibody as a new type of therapeutic intervention in the treatment of asthma. Lukacs *et al.* teach the administration a TNF receptor to SEA-challenged mice, but not the administration of an anti-TNF antibody. Rudmann *et al.* and Matheson *et al.* provide evidence that one of ordinary skill in the art would not have been able to reasonably predict with an expectation of success, given the teachings of Lukacs *et al.*, whether administration of an anti-TNF antibody to a subject would be effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma. As such, the cited combination of the Le '195 patent, Shah *et al.* reference and

Lukacs *et al.* references would not have suggested to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success, Applicant's claimed method of treating asthma, Applicant's claimed method of treating airway inflammation associated with asthma or Applicant's claimed method of reducing accumulation in lungs of inflammatory cells associated with asthma. In addition, submitted herewith is an executed Declaration of Don E Griswold, Ph.D., under 37 C.F.R. § 1.132, which addresses the Le '195 patent, Shah *et al.* reference and Lukacs *et al.* reference. Thus, the claimed invention is not *prima facie* obvious in view of the cited combinations of references.

Reconsideration and withdrawal of the rejection of Claim 1-12 under 35 U.S.C. § 103 are respectfully requested.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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